IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Shipman	
Application No.: 09/786,105	
Filed: 2/26/2001	Group Art Unit: 1637
Title: Method and kit for the characterization of antibiotic-resistance mutations in mycobacterium tuberculosis	Examiner: Suryaprabha Chunduru
	Confirmation No.: 8468
Attorney Docket No.: VGEN.P-055	

BRIEF FOR APPELLANT

This brief is filed in support of Applicants' Appeal from the final rejection mailed 2/3/2003. Consideration of the application and reversal of the rejections are respectfully urged.

Real Party in Interest

The real party in interest is Bayer Healthcare LLC.

Related Appeals and Interferences

To Applicants' knowledge, there are no related appeals or interferences.

Status of Claims

Claims 1-13 and 15-21 have been canceled. Claim 14 remains pending and is the subject of this appeal.

Status of Amendments

All amendments have been entered.

Summary of Invention

The invention claimed in this application relates to a kit for evaluation of antibiotic-resistance mutations in a sample of *Mycobacterium tuberculosis.* A defined in claim 14, the kits comprise pairs of amplification primers and matched pairs of sequencing primers for amplification and sequencing, respectively, of at least the rpoB, katG, rpsL/s12 and 23S genes of *M. tuberculosis.* The amplification and sequencing primer pairs in the kit include at least one combination of an amplification primer pair and a matched sequencing primer pair for amplification and sequencing of a common gene that is selected from a list. Each member of the list identifies by sequence ID numbers the amplification primers (2) and the sequencing primers (2) for a particular gene.

Issues on Appeal

Would the claimed invention have been obvious, and therefore unpatentable under 35 USC § 103, over the combination of references cited by the Examiner?

Applicants submit that this question should be answered in the negative, and that the rejection of claim 14 should therefore be reversed.

Grouping of Claims

There is only one claim in this application, which is addressed as a single group.

Argument

Claim 14 stands rejected as unpatentable under 35 USC § 103 over WO95/33851 in view of US Patent No. 5,851,763 and US Patent No. 5,985,569. Applicants submit that this combination of references does not suggest any of the specific combinations of primers which are the subject of claim 14, and that the rejection amounts to nothing more than an invitation to experiment. An invitation to experiment, however, is not sufficient to support a rejection under 35 USC § 103. Thus, the rejection should be reversed.

The Teachings of the Cited Art

WO95/33851 teaches primers for evaluation of antibiotic resistance in mycobacteria, and teaches a sequence that matches Seq. ID Nos. 1 and 3, which are half the amplification and sequencing pairs in the first alternative listed in claim 14, which are sequences used in amplification and sequencing of the rpoB gene. As acknowledged by the Examiner, WO95/33851 does not teach Seq ID Nos 2 and 4, which are the other half of the claimed primer pairs.[1]

US Patent No. 5,851,763 also relates to mycobacterium, and discloses the complete sequence of the rpoB gene. Necessarily, since primers 2 and 4 are complementary to this gene sequence the sequence of these primers can be found within the larger sequence, but these primers are not specifically disclosed in the '763 patent.

US Patent No. 5,985,569 relates to primers for use in species identification of mycobacterium based on the sequence of the 16S ribosomal RNA (not the rpoB gene which is the elected species and the subject of the other references). None of the primers disclosed in the '569 patent are the same as those claimed in this application. The portion of the patent that the Examiner relies on is a computer program that designs primers. As stated in the '569 patent:

> A computer program, OLIGO-PROBE DESIGN STATION (AGCT Inc., Irvine, Calif.), was used to design SDA primers and bumpers derived from the mycobacterial 16S rRNA gene with the desired characteristics. This program identifies candidate probe sequences from every location of the target gene of interest based on melting temperature (Tm) of the probe. If the target gene is 100 bp, for example, the computer extracts approximately 100 potential probes, one starting from each nucleotide base in the target gene and selects those that satisfy the specified Tm criteria. As Tm represents the actual binding strength of hybridization and stringency of assay conditions, two probes with the same Tm, or similar Tm, can provide high sensitivity and selectivity as a primer pair.

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[1] It is noted that Seq. IDs 1 and 3 have the same sequence, as do Seq. ID Nos. 2 and 4. They are delineated as separate sequence numbers for clarity, since the non-DNA portion of the sequences can distinguish between the primer when used for amplification and when used for sequencing.

> Each candidate probe was analyzed for potential hybridization against sequences in the GenBank Bacterial Database using an algorithm for homology analysis. In a homology calculation for mismatched probes, the program calculated Tm at the longest non-mismatched stretch of nucleotide sequences. This screening process identified all sequences in the database that may hybridize to each candidate probe. From these data, probe sequences having identity to 16S rRNA sequences from the Mycobacterium species of interest were identified.
>
> Probe sequences showing identity with numerous species of Mycobacterium were then screened for cross-reactivity with non-Mycobacterium species. The screening strategy consisted of comparing the probe sequences against sequences in the GenBank Bacterial Database and against sequences in smaller databases containing only genes from suspected cross-reactant species. From these screenings, probes were selected that should hybridize to all of the Mycobacterium species of interest, but not to any non-Mycobacterium sequences.

'569 Patent, Col. 13, line 48-Col. 14, line 17.

The Examiner's Argument

As stated in the Official Action mailed August 14, 2002, the Examiner asserts that it would have been obvious "to combine the sequences of primer taught [in WO95/33851] with the primer selection sequence as taught by [the secondary references] which is well known in the art at the time the invention was made." In the Final Rejection mailed February 3, 2003, the Examiner stated that Applicants' argument that the "combination of primers of the instant invention are non-obvious and hence [that] the general techniques described in the prior art of record are not relevant to the present context ... is not persuasive because one having ordinary skill in the art would know how to design a primer or primers using currently available techniques." Finally, in the Advisory Action mailed July 1, 2003, the Examiner stated that

> the technique to make the primer or end result is obvious at the time the invention was made and hence the product developed based on the known technique, that is oligo-design station [('569 patent)] would be obvious... Once the target gene sequence is known it is obvious to design a proper combination of primers flanking the target site to amplify the target.

The Applicable Law

35 USC § 103 states, *inter alia*, that the patentability of an invention shall not depend, or be negatived, by the manner in which the invention is made. This provision has manifested itself in case law as limitations on what is sufficient to conclude that an invention would have been obvious. One group of cases deals with the concept that an invention that is merely "obvious-to-try" is not obvious under § 103. The law as it relates to obvious-to-try type rejections was summarized by the Court of Appeals for the Federal Circuit in *In re O'Farrell,* 7 USPQ2d 1673 (Fed Cir. 1988). There, the Court observed that:

> The admonition that "obvious to try" is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. *E.g .*, *In re Geiger*, 815 F.2d at 688, 2 USPQ2d at 1278; *Novo Industri A/S v. Travenol Laboratories, Inc .*, 677 F.2d 1202, 1208, 215 USPQ 412, 417 (7th Cir. 1982); *In re Yates*, 663 F.2d 1054, 1057, 211 USPQ 1149, 1151 (CCPA 1981); *In re Antonie*, 559 F.2d at 621, 195 USPQ at 8-9.

7 USPQ2d at 1781.

In a similar vein, the Court of Customs and Patent Appeals reversed a § 103 rejection in the case of *In re Kratz*, 201 USPQ 71 (CCPA 1979). In *Kratz*, the Court was confronted with a case in which the claimed invention was a compound that provided the taste and smell of strawberries. Because the compound was an isolate from strawberries, and because the Examiner and the Board of Appeals considered analyzing strawberries an obvious approach to finding the key flavor ingredient, the composition claim was rejected. The CCPA reversed, observing that an obvious method of arriving at result does not make result arrived at obvious.

The Examiner's Position is Inconsistent with Law and Fact

The claims of this application relate to **specific combinations of primers**, and it is the patentability of these **combinations of primers**, not primers for the target gene[2] generally, which must be considered. Nothing in the art, nor in the Examiner's arguments, points to these specific primer combinations.

As is clear from the references cited, using algorithmic procedures to arrive at possible primer sequences results not in one or two sequences, but a multiplicity of sequences. Applicants claim only specific primer pairs that are adapted to actually work together. This is important because it is technically inaccurate to assume that any and all primers work for amplification and sequencing with equal efficiency. For example, as shown in US Patent No. 6,228,577, a copy of which is attached as Exhibit A, shifts of only a few bases in the position of a sequencing primer can make substantial differences in the quality of the sequencing results obtainable. Different primers work better than others, and different primer combinations work better than others. The primer sets recited in claim 14 were selected to work well with the other primers in the identified combination. Thus, the Examiner should base any rejection of a specific primer sequence on something more than a complete sequence and an invitation to experiment to find workable primer pairs within that sequence. The Examiner has not provided that "something more" here.

The Examiner has not looked at the art and indicated how the algorithmic approach of the '569 patent would necessarily arrive at primers 2/4 to use in combination with primers 1/3. He further has not said why he would expect primers 2/4 to be the only primers, or even one of a very few primers proposed by the algorithm. Instead, notwithstanding the fact that '569 patent looks at 1 probe for every base pair and reduces this number based on Tm to some smaller number that then have to be further tested; and that with possible variations in probe length that the number of possible probes could be enormous, the Examiner just states that the particular primers of claimed invention would have been obvious. Thus, the Examiner has

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[2] The rpoB gene in the case of the elected species

failed to show that the references provide "a roadmap which would have directed a person having ordinary skill in the art to" the specific sequences of claim 14 which was the standard required in *Ex parte Goldgaber*, 41 USPQ2d 1172, 1176 (POBAI 1995). Furthermore, he has not taken into account that it is not a single primer which is claimed, but a primer pair which must work together to provide adequate amplification and/or sequencing. This failure to look at the claimed invention as opposed to a more general concept is improper and mandates the reversal of the rejection.

Both the statute and the case law make it clear that the methodology by which an invention is arrived at is not relevant to the question of whether an invention is obvious. The Examiner states that exact opposite as support for the rejection. The case law states that a claim directed to specific compounds is not rendered obvious by art that suggests varying many parameters to see if something works. The Examiner argues the opposite, that the possibility of many different primers is not relevant to the patentability of the specific primer combinations that are claimed.

One case of importance in this regard is *In re Deuel* 34 USPQ2d 1210 (Fed. Cir. 1995). In *Deuel* the Federal Circuit observed that "because Deuel claims new chemical entities in structural terms, a *prima facie* case of unpatentability requires that the teachings of the prior art suggest the claimed compounds to a person of ordinary skill in the art." 34 USPQ2d at 1214. The Court continued noting that:

> The PTO's theory that one might have been motivated to try to do what Deuel in fact accomplished amounts to speculation and an impermissible hindsight reconstruction of the claimed invention. It also ignores the fact that claims 5 and 7 are limited to specific compounds, and any motivation that existed was a general one, to try to obtain a gene that was yet undefined and may have constituted many forms. A general motivation to search for some gene that exists does not necessarily make obvious a specifically-defined gene that is subsequently obtained as a result of that search. More is needed and it is not found here.

Id. at 1215. Ironically, the Examiner has cited *Deuel* in support of his rejection, when it in fact shows the error of the rejection.

The rejection is clearly premised on a general motivation to search for some primer that will work. Paraphrasing *Deuel*, this does not necessarily make obvious a primer, or in this case a primer pair, located as a result of this search. Since the Examiner has offered nothing more, there is no *prima facie* case, and the rejection should be reversed.

Conclusion

In view of the errors discussed above, Applicants submit that the claims of this application are allowable over the cited art. Reversal of the rejection and return to the Examiner for consideration of the full scope of the claim, beyond the elected species, is respectfully urged.

Respectfully submitted,

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APPENDIX
CLAIM ON APPEAL

14. A kit for evaluation of antibiotic-resistance mutations in a sample of *Mycobacterium tuberculosis*, comprising pairs of amplification primers and matched pairs of sequencing primers for amplification and sequencing, respectively, of at least the rpoB, katG, rpsL/s12 and 23S genes of *M. tuberculosis*, wherein the amplification and sequencing primer pairs in the kit include at least one combination of an amplification primer pair and a matched sequencing primer pair for amplification and sequencing of a common gene selected from among the following combinations of primer pairs:

(a) amplification primers of Seq. ID Nos. 1 and 2 in combination and sequencing primers of Seq. ID Nos. 3 and 4;

(b) amplification primers of Seq. ID Nos. 6 and 7 in combination and sequencing primers of Seq. ID Nos. 8 and 9;

(c) amplification primers of Seq. ID Nos. 11 and 12 in combination and sequencing primers of Seq. ID Nos. 13 and 14;

(d) amplification primers of Seq. ID Nos. 16 and 17 in combination and sequencing primers of Seq. ID Nos. 18 and 19;

(e) amplification primers of Seq. ID Nos. 21 and 22 in combination and sequencing primers of Seq. ID Nos. 23 and 24;

(f) amplification primers of Seq. ID Nos. 26 and 27 in combination and sequencing primers of Seq. ID Nos. 28 and 29;

(g) amplification primers of Seq. ID Nos. 31 and 32 in combination and sequencing primers of Seq. ID Nos. 33 and 34;

(h) amplification primers of Seq. ID Nos. 36 and 37 in combination and sequencing primers of Seq. ID Nos. 38 and 39;

(i) amplification primers of Seq. ID Nos. 41 and 42 in combination and sequencing primers of Seq. ID Nos. 43 and 44; and

(j) amplification primers of Seq. ID Nos. 46 and 47 in combination and sequencing primers of Seq. ID Nos. 48 and 49.